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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/860,348	05/16/97	HEATH A	225/-1-001

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EXAMINER	
GAMBEL, P	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 05/27/98

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/878,348	Heath et al.
Examiner	**Group Art Unit**
GAMBEL	1642

☒ Responsive to communication(s) filed on *Feb 27, 1998*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-23* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-23* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *3*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. The location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1642, Technology Center 1600.

2. Applicant's election with traverse of Group I (claims 1-16) in Paper No. 5 is acknowledged. The traversal is on the ground(s) that the search and consideration for Groups I-III would be overlapping and that antigens of Groups I would be made by the method of Group II. Upon reconsideration and in view of compact prosecution as well as in view of the recombinant means of producing the vaccine/adjuvant as set forth in Group II, the nucleic acid of Group III would be required; all of the claims will be considered in the instant application.

3. Formal drawings and photographs have been submitted which fail to comply with 37 CFR 1.84. Please see the enclosed form PTO-948.

Applicant is reminded to change the Brief Description of the Drawings in accordance with these changes, if necessary.

4. The application is required to be reviewed and all spelling, TRADEMARKS, and like errors corrected.

Trademarks should be capitalized or accompanied by the ™ or ® symbol wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the trademarks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

5. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. The specification is objected to and claims 2-21 and 23 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention. In evaluating the facts of the instant case, the following is noted:

In vitro and animal model studies have not correlated well with in vivo clinical trial results in patients. Since the therapeutic indices of vaccines can be species- and model-dependent, it is not clear that reliance on the limited experimental observations with survival of certain immunized mice with S. Pneumoniae type II challenge accurately reflects the relative efficacy of CD40L and anti-CD40 antibodies in the breadth of vaccines encompassed by the claimed methods and compositions.

Page 6, paragraph 2 of the instant specification discloses that vaccine is intended to include a wide variety of vaccines including, but not limited to, contraceptive vaccines, immunotherapy vaccines and prophylactic or therapeutic vaccines. However, ability to generate protective or therapeutic responses encompassed by the breadth of antigens and parts thereof in the vaccines encompassed by the claimed invention is a vaccine is not predictive. There is insufficient guidance and directions as to the selection of appropriate TD or TI antigens as well as parts thereof in provide the appropriate immunization to achieve vaccination commensurate in scope with the claimed vaccines, antigens and parts thereof. The specification does not adequately teach how to make and use TD or TI antigens and parts thereof commensurate in scope with the disclosed vaccines, encompassed by the claimed invention. The specification does not teach how to extrapolate data obtained from limited experimental observations with mice with one antigen system to the development of effective vaccines and methods to make said vaccines, commensurate in scope with the claimed antigens and parts thereof. There is insufficient objective evidence provided that the claimed vaccines and methods of making said vaccines would induce protective immunity against the breadth of antigens encompassed by the claimed invention. It is noted that generating an immune response does not necessarily mean that is capable of generating the immunoprotective response need to meet the definition or scope of a vaccine. The scope of the claims must bear a reasonable correlation with the scope of enablement. Without such guidance, the nature of the structure of TD/TI antigens and parts thereof which can provide sufficient vaccination is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

In view of the lack of predictability of the art to which the invention pertains the lack of established protocols for effective vaccines against the breadth of TD/TI antigens encompassed by the claimed methods and disclosed in the specification as filed; undue experimentation would be required to practice the claimed compositions and methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed compositions and methods, absent working examples providing evidence which is reasonably predictive that the claimed vaccines and methods of making said vaccines are effective in treating the breadth of TD/TI antigens, encompassed by the claimed invention.

It is noted that the claims are drawn to vaccines and not just the use of CD40 ligand or CD40-specific antibodies as adjuvants.

7. Claims 1-23 are rejected under 35 U.S.C. § 112, first and second paragraphs, as the claimed invention is not described in such full, clear, concise and exact terms as to enable any person skilled in the art to make and use the same, and/or for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The instant claims are indefinite and ambiguous in the recitation of "adjuvant which is adapted to stimulate a B lymphocyte cell surface receptor, CD40", "wherein said adjuvant is a CD40 ligand or part thereof" , "wherein said adjuvant is an antibody raised against said CD40 receptor or a part thereof" because the defining structural features of the adjuvants are either not known (e.g. claim 1 and dependent claims) or ill-defined and ambiguous. There is insufficient guidance or direction as to either the meaning or the metes and bounds of "adjuvants" as well as "parts thereof".

Further, it is noted that the use of "CD40 receptor" is ambiguous as it appears that the intent of this phrase is drawn to CD40 itself, while the recitation of "CD40 receptor" could read on a receptor of CD40 and not CD40 itself. Applicant is invited to recite "CD40" or "CD40 ligand" and to avoid the use of "CD40 receptor" in the interest of clarity.

In addition, while "adjuvant" and "part(s) thereof" may have some notion of activity or structure, there is nothing in the claims which distinctly claims or sets forth the metes and bounds of the "adjuvant" or "part(s) thereof". The instant claims fail to distinctly claim what that "adjuvant" or the "part(s) thereof" are made up of. Also, it is noted that the recitation of "or a part thereof" in claim 5 could read on either the "antibody" or the "CD40 receptor" (CD40)..

There is insufficient direction and guidance with respect to "adjuvant which is adapted to stimulate a B lymphocyte cell surface receptor, CD40", "wherein said adjuvant is a CD40 ligand or part thereof" , "wherein said adjuvant is an antibody raised against said CD40 receptor or a part thereof".

Applicant has not enabled or provided written description of any "adjuvant which is adapted to stimulate a B lymphocyte cell surface receptor, CD40". It is noted the specification discloses that the instant adjuvant includes references to any string of amino acids or ligand which is selected so as to bind to at least a part of CD40 (page 8, paragraph 1). There is insufficient direction and guidance as well as written description as to the scope of such "string of amino acids". Further for the reasons set forth herein, it is not sufficient to simply bind to at least a part of CD40 to provide for adjuvant properties, as encompassed by the claimed invention. For example, there are both agonistic and antagonistic CD40-specific antibodies and agonistic antibodies need to be cross-linked in some manner to provide augmentation of the immune response and lymphocyte signaling.

With respect to the CD40 ligand, WO 93/08207 discloses that membrane bound CD40L and oligomeric CD40L (dimeric or trimeric) are useful as CD40 agonists, while monomeric CD40L is useful as a CD40 antagonist (see entire document, including page 12, paragraph 1). There appears insufficient guidance and enablement for the use of adjuvants comprising CD40 ligand, wherein the CD40L is not at least oligomeric and preferably trimeric. Mazzei et al. (J. Biol. Chem. 270: 7025, 1995); the trimeric conformation of the CD40 ligand may be required for binding to CD40 and its ability to stimulate via CD40 that is indistinguishable from the membrane bound from of the protein (see entire document, including Abstract and Discussion). While functional soluble forms of recombinant CD40L have been produced, it was known at the time the invention was made that a CD40L-IgG1-Fc fusion proteins which exists as a disulphide-linked dimer has low activity on B cells and required additional cytokines for B cell proliferation under defined culture conditions.

Therefore it would be expected that "parts" of CD40L or targeting only parts of CD40 (CD40 receptor) would not result in sufficient signaling associated with the claimed adjuvants. In contrast, it would be expected that "parts of CD40L or targeting "parts of CD40" would serve to antagonize the activity of lymphocyte responses. There appears insufficient guidance and direction as to enablement and written description of the claimed "adjuvants", "parts of CD40 ligand" or targeting "parts of CD40", commensurate in scope with the claimed invention. Applicant has not enabled such adjuvants with CD40L or antibodies that bind CD40 that do not have the appropriate conformation or sufficient multivalency to stimulate lymphocyte responses, associated with the properties of an adjuvant.

It was known at the time the invention was made that sufficient stimulation via CD40 required cross-linking of CD40 via CD40-specific antibodies or CD40 ligand in combination with appropriate lymphokines. In applying CD40 ligand, cross-linking occurred via transfected or surface-bound CD40 ligand. There is insufficient guidance and direction to enable adjuvants adapted to stimulate a B lymphocyte cell surface receptor CD40 and the production of said adjuvants other than providing CD40 ligand as oligomers and particularly trimers or polypeptides having the appropriate multivalency or providing CD40-specific antibodies in a manner that induces appropriate immune responses in vivo.

In view of the lack of predictability of the art to which the invention pertains the lack of established protocols for effective adjuvants, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed compositions and methods and absent working examples providing evidence which is reasonably predictive that the claimed compositions and methods are effective as an adjuvant.

The amendments must be supported by the specification so as not to add any new matter.

8. Claims 5-7 and 14-21 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 5-7 are indefinite in the recitation of "CD40 receptor" because it appears that the intention of this recitation is drawn to CD40 itself and not a receptor for CD40. Applicant is invited to recite "CD40" and not "CD40 receptor" when referring to CD40.

B) Claim 5 and dependent claims thereof are indefinite in the recitation of "or a part thereof" because it is not clear whether its antecedent basis is "antibody" or "CD40 receptor".

C) Claim 14, line 1 is indefinite in the recitation of "from", since it appears that "for" is the appropriate word.

D) Claim 14 does not further limited claim 2, since a vaccine would necessarily have to be formulated to be administered to an individual.

E) Claims 15-16 are indefinite in that it does not recite clear steps, particularly with respect to the "association or combination of said antigen with an adjuvant". The metes and bounds of this method is ambiguous and confusing. Applicant is invited to recited active, positive steps delimiting how this method is actually practiced

F) Claims 15-16 should delete the term "novel" since all allowed claims are presumed to be novel and unobvious.

G) Claims 17-21 are indefinite in the recitation of "a system for the manufacture", since it is not clear what is meant by a "system", nor are the metes and bounds readily discernable. It appears that the claims are drawn to a method of manufacturing a vaccine, comprising recombinant cells in contrast to a composition per se. Applicant should recite clear method steps and ingredients and amend the preamble accordingly. Applicant is invited to recited active, positive steps delimiting how this method is actually practiced

H) The applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

10. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

11. Claims 1-3, 5-6, 8, 10, 11-12 are rejected under 35 U.S.C. § 102(a) as being anticipated by Dullforce et al. (1449, #AA). Dullforce et al. Teach vaccinating with CD40-specific antibodies and polysaccharide (see Abstract). Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced CD40-specific antibodies and their use as adjuvants.

11. Claims 1 and 22 are rejected under 35 U.S.C. § 102(a)(e) as being anticipated by Aruffo et al. (U.S. Patent No. 5,540,926). Aruffo et al. teach the use of mouse and human gp39 (i.e. CD40 ligand), including recombinant gp39 proteins and soluble gp39 fusion proteins as an adjuvant to increase an immune response to a vaccine (see entire document, including column 11, paragraph 7). Aruffo et al. also teach that soluble human gp39 forms dimers and trimers in solution (column 17, lines 15-18) as well as recombinant expression of said gp39 in vaccinia viral vectors (column 7, paragraph 2). Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced gp39 constructs and their use as adjuvants. A composition is a composition irrespective of what its intended use is. See In re Tuominen, 213 USPQ 89 (CCPA 1982).

12. Claims 1 and 22 are rejected under 35 U.S.C. § 102(e) as being anticipated by Armitage et al. (WO 93/08207). Armitage et al. Teaches the recombinant expression of CD40L polypeptides as vaccine adjuvants in various expression systems (see entire document, particularly pages 20-25). The claimed functional limitations would be inherent properties of the referenced gp39 constructs and their use as adjuvants. A composition is a composition irrespective of what its intended use is. See In re Tuominen, 213 USPQ 89 (CCPA 1982).

13. Claim 1 is rejected under 35 U.S.C. § 102(b) as being anticipated by Ledbetter et al. (U.S. Patent No. 5,247,069). Ledbetter et al. Teaches the use of Bp50-specific antibodies as adjuvants (see entire document, particularly Summary of the Invention, and Section 5.4.1). The claimed functional limitations would be inherent properties of the referenced Bp50-specific antibodies and their use as adjuvants. A composition is a composition irrespective of what its intended use is. See In re Tuominen, 213 USPQ 89 (CCPA 1982). It was known at the time the invention was made that the Bp50-specific antibodies taught by Ledbetter et al. were specific for CD40, that is, Bp50 and CD40 are the same antigen specificity.

16. Claims 1-23 are rejected under 35 U.S.C. § 103 as being unpatentable over Aruffo et al. (U.S. Patent No. 5,540,926) AND/OR Armitage et al. (WO 93/08207) AND/OR Ledbetter et al.(U.S. Patent No. 5,247,069) AND/OR Dullforce et al. (1449, #AA) in view of art known methods of making and providing vaccine formulations to various antigens, as acknowledged by applicant in their traverse response to the restriction requirement, filed 2/27/98 (Paper No. 5), as acknowledged by applicant's specification where it is stated that "it should be apparent to those skilled in the art that this methodology may also be applied to any antigens" (page 7, lines 1-2) and in view of Noelle (Immunity, 1996), Mond et al. (U.S. Patent No. 5,585,100), Scott et al. (U.S. Patent No. 5,723,127)Marburg et al. (U.S. Patent Nol. 5,623,057).

The instant claims are drawn to methods of making vaccines and vaccines preparations encompassing the use of CD40L or CD40-specific antibodies as adjuvants.

The teachings of Aruffo et al. (U.S. Patent No. 5,540,926) AND/OR Armitage et al. (WO 93/08207) AND/OR Ledbetter et al.(U.S. Patent No. 5,247,069) AND/OR Dullforce et al. (see entire documents) are set forth above. It is noted that both Aruffo et al. and Armitage et al. Teach the recombinant expression including the production of soluble forms of CD40L. Although these references teach the use of CD40L or CD40-specific antibodies as adjuvants for vaccines or to boost immune responses in various individuals, they differ from the instant claims by not disclosing all of the art practiced methods and formulations of making said vaccines comprising an adjuvant nor do they disclose the art known combination of an adjuvant with an antigen of interest.

Further and as noted above, both applicant's response to the restriction requirement and the specification as filed indicate that vaccine formulations and methods of making said vaccines comprising an adjuvant, as encompassed by the dependent claims were all well known and practiced by the ordinary artisan at the time the invention was made.

It is clear that the primary references teach the use of CD40L or CD40-specific antibodies as adjuvants to stimulate the immune response, including B cells responses and that the various dependent limitations were all well known vaccine formulations and methods of making said vaccine formulations at the time the invention was made by the ordinary artisan.

In addition to the teachings of the primary references, Noelle et al. Teach the importance of CD40 and the CD40 ligand in host defense against a wide variety of antigens, encompassing the T dependent and T independent antigens encompassed by the claimed invention.

In addition, the following references provide art known teachings of various methods or making vaccine formulations and the vaccine formulations themselves, as encompassed by the claimed invention.

Mond et al. Teach the methods of making and the use of dual carrier immunogenic constructs as vaccines to both T dependent and T independent antigens, wherein said constructs comprise substances that stimulate the immune response, including B cells responses (see entire document).

Scott et al. Teach the methods of making and the use of cytokines in vaccine formulations to a variety of antigens, including combining antigen or recombinantly expressing antigen in said formulations (see entire document).

Marburg et al. Teach the methods of making and the use of polysaccharide antigens in vaccine constructs (see entire document).

As well known and practiced at the time the invention was made, as acknowledged by applicant and as taught by the combination of primary and secondary references, the ordinary artisan had various means to make and formulate vaccines to a number of antigens, including both TD and TI antigens. The nucleic acid molecules as well as humanized antibodies encompassed by the claims would have been generated by making recombinant forms of said vaccines. Also, humanized antibodies would have been used to be less immunogenic to the antibody per se. Similarly, making vaccines as fusion proteins or with secretion signals, as taught and known by the prior art, would have been generated by making recombinant forms of said vaccines. The ordinary artisan was motivated at the time the invention was made to make and use such vaccines, including recombinant forms of said vaccines, with adjuvants that could stimulate immune responses, including B cell responses to a variety of antigens. Given the teachings of Aruffo et al., Armitage et al., Ledbetter et al. and Noelle; it was readily apparent that signaling via CD40, which was expressed on B cells as well as antigen presenting cells, was important to the host defense against a plethora of agents, encompassing TD and TI antigens. Therefore, it would have been obvious to the ordinary artisan at the time the invention was made to apply adjuvants comprising CD40 ligand or CD40-specific antibodies in a number of art practiced and known vaccine formulations to a variety of TD and TI antigens. Given the importance of signaling via the CD40 pathway, the ordinary artisan would have had an expectation of success in stimulating immune responses to a variety of antigens.

Given the claims are given their broadest interpretation; the claimed compositions, methods of manufacturing a vaccine and a system of manufacturing a vaccine appear to read on providing CD40L or CD40-specific antibodies in known vaccine formulations or making vaccines with adjuvants in known methods to increase the immune response. The prior art teaches the use of CD40L and CD40-specific antibodies to act as an adjuvant in various individuals to a variety of antigens.

Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to select the CD40L or CD40-specific antibodies to make and use vaccine formulations to stimulate immune responses to a variety of antigens, encompassed by the claimed methods. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

17. No claim is allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lila Feisee can be reached on (703) 308-2731. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7939.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to **[lila.feisee@uspto.gov]**.

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

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May 26, 1998